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Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997–2003

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Aims
To describe trends in utilization and prescribing of statins and other lipid lowering drugs across Europe from data in routine administrative databases.

Methods
Observational study in EU member states and Norway. Comparison of annual utilization data for lipid lowering agents by class and drug from national administrative databases for reimbursement over the period 1997–2003, measured in DDDs per 1000 inhabitants/day. Prescribed daily doses (PDD) of statins obtained from a commercial database (IMS Health) for 2000 and 2003, and used to calculate numbers of 'patient treatment days' (PTD) in each country in each year. Analysis of PTD to explain increased utilization of statins.

Results
Use of lipid lowering agents varied among countries (in 2003, highest in Ireland and Norway, and lowest in Italy), but increased in all countries studied (between 2000 and 2003 by 274% in Ireland and by 56% in France). This increase was entirely due to increases in statin use. Prescribed daily doses of statins increased in all countries for which data was available between 2000 and 2003, but still usually fell below the doses used in the major trials of statins. As a result, the numbers of PTDs increased to a lesser extent than suggested by utilization (e.g. by 192% in Ireland and by 35% in France). One-third of the total rise in utilization was explained by increased PDD, and two-thirds by an increase in numbers of PTDs. Statins dominated the markets in all countries, although fibrates remained strong in France and Belgium (approximately 25% of all lipid lowering agents) and to a lesser extent Germany (10%).

Conclusions
Use of statins across Europe has increased hugely over the study period. Some of the increase in use is due to higher prescribed daily doses, but two-thirds is due to increases in numbers of patient days of treatment, either due to more patients treated or less likely to better compliance.

Introduction

Coronary heart disease remains the major cause of death in many European countries, although there are substantial variations [1]. Extensive public health measures are directed at either preventing or treating it. Lipid lowering agents (LLA) are widely used in most European countries to try to reduce the relative risk of coronary events [2]. Statins dominate the market, a testament to their efficacy as demonstrated in several studies showing a reduction in mortality in high-risk groups, and their

tolerability. In some countries, other agents such as fibrates remain important. Comparative data on the utilization and costs of statin market have been previously published as a snapshot in time [3, 4]. However this market is rapidly changing. When statins were first launched, public health efforts focused on thresholds for initiating treatment, encouraging treatment of more patients. Now in addition there is emphasis on the target cholesterol to be attained [5–7], which involves treating individual patients more aggressively with higher doses of drugs. Either of these trends will increase the use of lipid lowering agents, but their relative extent is unclear.

Previous studies demonstrated the feasibility of using data from administrative databases to compare utilization across countries [2, 8], and their reliability compared with a standard commercial source [3]. We explored the changes in the utilization of lipid lowering agents in western European countries over the period 1997–2003 using administrative and commercial databases.

Methods

We collected annual data on statins and other lipid lowering agents in European Union countries and in Norway for the years 1997–2003. The administrative data were obtained from the major publicly supported sources, mostly governmental, or major insurance/sickness funds: these have been described in detail previously [2]. These systems cover usually only the publicly funded use in the community. Depending on the nature of drug reimbursement in each country, the database may cover all or only part of a population. For instance, the Irish data refer only to the population covered by the General Medical Services Scheme (1 148 055 patients in 2000, or one-third of the total population [9], based on age or low income); for France, Germany, Netherlands and Portugal, the data refer to the population covered by social insurances or the publicly funded health service (from 70 to 90% of the whole population, according to the country); 'UK' data refer to England only (83% of UK population).

Data on prescribed daily doses (PDDs) for statins only were obtained from a commercial database (IMS) for the years 2000 and 2003. IMS collects and interprets anonymized health information from a number of sources but for this study, the key source is a sample of doctors practising in office-based locations in each country (Appendix 1). The doctors contributing to the survey are chosen on the basis of the principles of random and stratified sampling. The sample covers both generalists and specialists where appropriate. The doctors report on every consultation for 1 week in every quarter. The exception to this is the UK where data are collected directly from GP computer systems. In Germany, paper reporting is also supplemented by information collected directly from GP systems.

Drugs studied were the statins (ATC code CA10AA); simvastatin, lovastatin (available only in eight countries), pravastatin, fluvastatin, atorvastatin, cerivastatin (withdrawn for safety reasons in August 2001), and rosuvastatin (available in only four countries by 2003); and other lipid lowering agents, mainly fibrates (CA10AB) but also bile acid sequestrants (C10AC), nicotinic acid derivatives (C10AD) and others (C10AX).

Main outcome measures were:

1 Utilization measured by total defined daily doses (DDD [10], and subsequently calculated per 1000 population covered by each national database per day
2 Prescribed daily doses (PDD), calculated as follows:
   a. For each drug and at each strength of tablet (e.g. simvastatin 10 mg tablets), the number of prescriptions was recorded noting the quantity (in numbers of tablets) and the numbers of times per day (usually once for statins). From this, an average daily number of tablets for that dose form was derived.
   b. The total number of doses per day for each strength of tablet was estimated by multiplying total prescription numbers by the average daily dosing for each form.
   c. This was converted into total milligrams per day by multiplying number of tablets for each form by the relevant strength.
   d. These were summated for all dosage forms and divided by the total numbers of prescriptions to give an average prescribed daily dose for that drug. Prescriptions without a clearly stated dose were disregarded.
3 Each drug has its own PDD at each time point. The number of days of treatment provided for each drug (patient treatment days, PTD_{200x}), i.e. numbers of patient treated for one day per 1000 population, is calculated as:

$$\frac{PTD_{200x}}{1000/day} = DDD/1000INH/day \times \frac{DDD}{PDD_{200x}}$$

The total number of PTD in each country in each year is the sum of the individual drugs' PTD. A worked example is shown in Appendix 2A. It is also possible to calculate how much of the increase in utilization is due to increased doses used or to increased numbers of PTD (Appendix 2B). These calculations were performed for each of the nine countries with PDD data for both years.

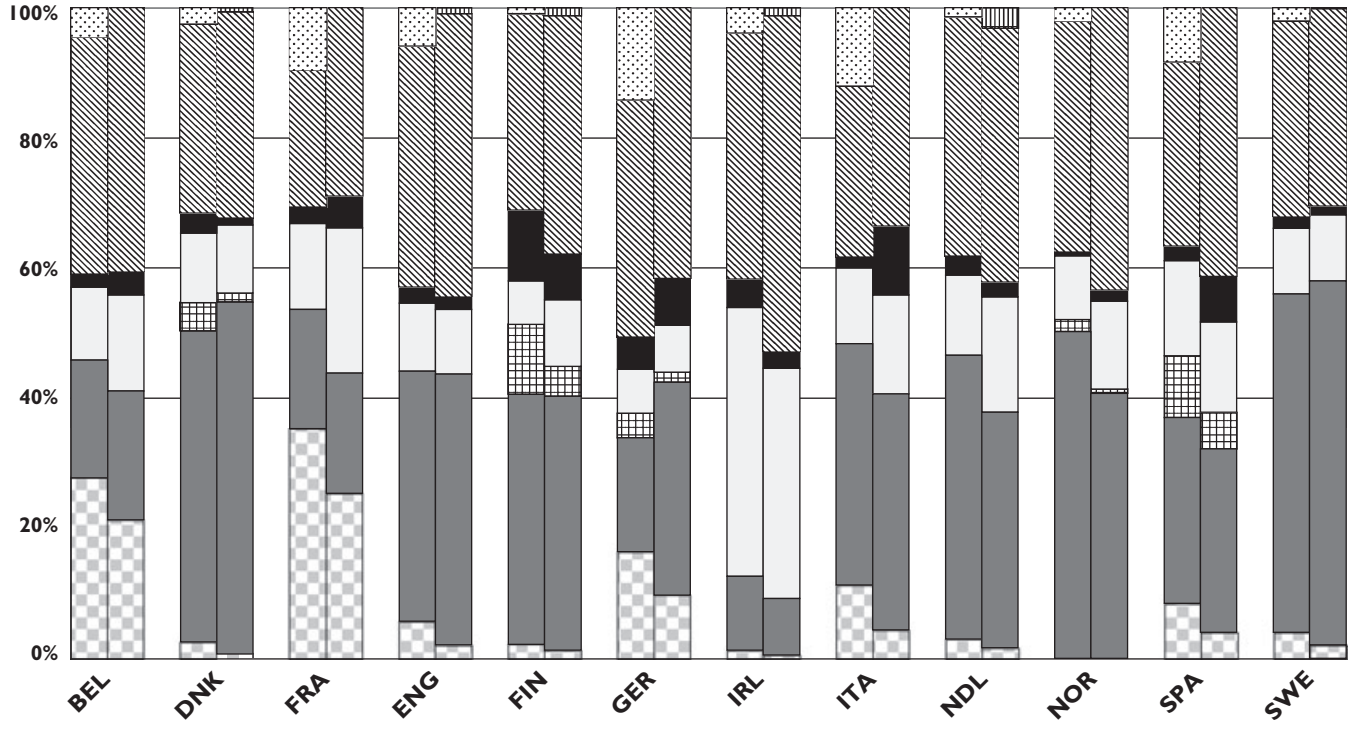

Figure 1

Market shares (%) of fibrates and different statins in 2000 (left bars) and 2003 (right bars) in 12 European countries; country abbreviations as in Appendix 1. Fibrates (▣), simvastatin (■), lovastatin (▦), pravastatin (□), fluvastatin (■), atorvastatin (⁙), cerivastatin (▨), rosuvastatin (▥)

Results

Administrative data were obtained for 13 European countries (Appendix 1), but not in each at all time points. No data were available for Luxembourg, Greece or Portugal. For Austria, only aggregated data on total use were available for both years.

Of these 13 countries, IMS data were not available for Denmark, Norway or Sweden (2003 only) as these are provided to IMS under licence and could not be made publicly available. We therefore obtained PDD data for both years for each drug for 10 countries; but because of lack of breakdown of data by drug in Austria, comparisons of PTDs/1000 could be made in only nine countries: Belgium, Finland, France, Germany, Ireland, Italy, Netherlands, Spain and the UK.

As described previously, there was extensive but variable use of these drugs across Europe. Statins dominated the market in all countries, accounting for 80% in some countries by DDD, but over 90% in most (Figure 1).

The use of statins increased over the years (Figure 2). The widest increase was in Ireland but this is distorted by the population covered by the Irish database (the oldest and sickest) who might be expected to be the heaviest drug users. The rates of rise varied among

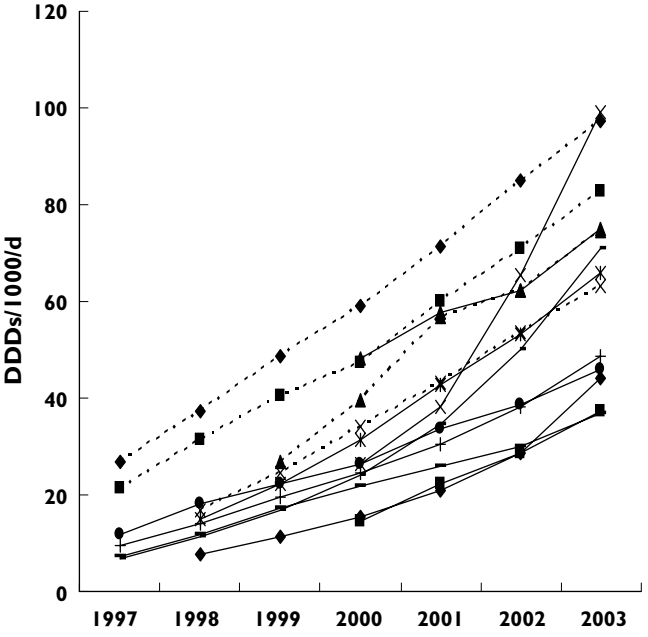

Figure 2

Increase in statin utilization. Norway (··♦··), Netherlands (··■··), Belgium (··▲··), Sweden (··×··), Finland (–✳–), Germany (–●–), Spain (–+–), UK (—), Austria (–), Denmark (–♦–), Italy (–■–), France (–▲–), Ireland (–×–)

countries – the median was 35.6% per year, annualized over the period 1999–2003; highest was Ireland at 54% per year, the lowest was France at 13.8% per year. The market leader varied in different countries, but the most common were simvastatin and atorvastatin. Apart from the disappearance of cerivastatin, there was little change in the relative share of the market between 2000 and 2003 (Figure 1).

PDDs were greater than DDD values in most cases (Table 1). There was considerable variation in the PDD by drug in each country with no consistent pattern. PDDs increased by varying amounts for each drug over the period 2000–2003.

PTD/1000 (Table 2) showed again wide variation among countries, with the highest levels in Ireland and the lowest in Italy. The increased utilization as measured

Table 1
Defined daily dose and average prescribed daily dose of statins in mg in the years 2000 and 2003

			Average prescribed daily dose (PDD) in mg								
Statin	Year	DDD mg	Belgium	England	Finland	France	Germany	Ireland	Italy	Netherlands	Spain
Simvastatin	2000	15	20.8	16.2	15.2	15.0	15.6	15.2	20.3	20.1	15.9
	2003	15	26.5	23.5	18.3	19.5	20.1	20.8	23.2	23.0	19.0
Lovastatin	2000	30	–	–	21.2	–	21.8	–	–	–	21.0
	2003	30	–	–	21.6	–	22.0	–	–	–	23.5
Pravastatin	2000	20	27.8	21.7	26.4	20.6	17.6	16.9	23.5	27.4	18.6
	2003	20	33.9	28.6	32.6	24.5	21.2	20.1	29.0	35.1	21.3
Fluvastatin	2000	40	42.5	51.1	27.0	37.5	30.9	28.4	39.0	37.2	32.7
	2003	40	67.0	36.8	54.2	51.2	51.4	44.3	73.3	51.1	60.1
Atorvastatin	2000	10	15.3	15.6	12.5	16.8	14.3	13.7	12.1	22.1	10.2
	2003	10	18.2	18.9	15.3	17.1	16.0	15.9	16.2	23.6	17.5
Cerivastatin	2000	0.2	0.28	0.19	0.30	0.28	0.25	0.16	0.19	0.23	0.19
	2003	0.2	–	–	–	–	–	–	–	–	–
Rosuvastatin	2000	–	–	–	–	–	–	–	–	–	–
	2003	10	–	12.90	10.50	–	–	10.40	–	13.60	–

Table 2
Statins utilization in 2000 and 2003 in nine countries

	Utilization in DDD/1000/day*			Number of patients treatment days per 1000 inhabitants (PTD)*			What percentage change in DDD/1000/day† is explained by . . .	
	2000	2003	% increase	2000	2003	% increase	Increase in PTD?	Increase in PDD?
Belgium	47.43	74.74	58	32.86	42.12	28	54	46
England	23.94	71.03	197	19.56	43.13	120	64	36
Finland	31.25	66.07	111	31.24	49.79	59	53	47
France	48.11	75.19	56	39.64	53.56	35	66	34
Germany	26.42	45.90	74	23.01	33.08	44	64	36
Ireland	26.54	99.29	274	26.51	77.43	192	71	29
Italy	15.02	37.12	147	12.38	23.45	89	69	31
Netherlands	48.70	82.90	70	31.42	45.74	46	63	37
Spain	24.36	48.73	100	26.46	35.92	36	64	36

**All drugs; †cerivastatin and rosuvastatin excluded (see text).*

by DDD was made up 60–70% by an increase in PTD/1000, and 30–40% by an increase in the PDD.

The use of fibrates (ATC code CA10AB) was far lower than that of statins in most countries (Figure 1). Their use was stable in the eight countries examined and by 2003 amounted to no more than 0.5% of statin use in Ireland, or 10% in Germany. However Belgium and France were exceptional: they showed a very high use of fibrates (mostly fenofibrate, some ciprofibrate) compared with other countries. This was also stable (Belgium 18.3 DDD/1000/day in 2000, 20.2 in 2003, France 26.3 in 2000, 25.5 in 2003) and the importance of fibrates was therefore declining proportionately as statin use increased, from 39 to 54% in 1999 to around 25% in 2003.

Other agents (CA10AC-C10AX) were very little used, though again stable. In most countries these accounted for no more than 0.1 DDD/1000/day. Exchange resins were used most in Sweden where their use and that of other drugs amounted to 0.3 DDD/1000/day.

Discussion

These data quantify the rise in the use of statins in the countries examined. Worldwide, the statins had the largest value of sales of any drug class in 2003 amounting to $22.7 billion with a growth of 14% over the previous 12 months [11]. This rise is not without its critics who feel that the effectiveness of statins is overstated and that their effect on public health less important, accounting for no more than 3% of the total fall in death rates from ischaemic heart disease in recent years [12, 13]. Internationally, there is no correlation between statin use and either deaths from ischaemic heart disease [14], or risk factors including cholesterol [15]. Large increases in the cost and volume of prescribing of lipid regulating drugs in the UK have been associated with only a modest decline in standardized admission ratios for acute myocardial infarction [16]. More study of real patient outcome data is required to assess the real impact and cost effectiveness of statins. A potential weakness of the databases we used is that it is not usually possible to link prescribing to a defined diagnosis and therefore we are unable to comment on targeting of statins to low- or high-risk patients in primary or secondary prevention: local audits would be needed to provide this information in most countries.

Despite these doubts, most physicians are convinced of their benefits and in some countries, there have been specific government policies to address the high rates of coronary heart disease, which have increased their use. In addition, these drugs have been very heavily marketed and there has been concern about misleading promotion in some countries such as France where overall ischaemic heart disease is among the lowest in Europe [17], and where the effectiveness of lipid lowering therapy as applied in primary care has recently been questioned [18]. Aggressive marketing of statins may be more important than a culture of evidence based medicine: for instance, atorvastatin was widely used long before it had trial evidence of reduction in cardiovascular mortality, which was only published in April 2003 [19].

The median increase in utilization (DDD/1000/day) was about 35% per year. This is explained for the most part by an increase in PTD/1000/day, suggesting either an increase in the numbers of patients treated or improvement in adherence to prescribed statins. Adherence to statins is well known to be poor in many countries [20]. A possible virtue of administrative databases is that where they record individual patient identities, it is possible to monitor compliance at the level of the individual patient, and to measure it across a population. For instance, Finnish data show that 359 200 (6.88% or 69 per 1000 of total population) patients received at least one prescription for a statin in 2003 [21]. From this and the data presented here, we can calculate that each patient received 0.96 DDDs or 0.723 PDDs per day per patient, i.e. compliance was 72.3%.

However, an increase in the PDD was also important, accounting for about one-third of the increase in overall utilization. The increase in PDD is due to either treating to achieve a specific cholesterol target (likely to require higher doses of statins than previously prescribed) in many patients [22] or to treating in line with the trials in which a clear patient benefit has been shown. Nevertheless, even by 2003, the PDDs were substantially below the doses used in such trials. This might in part explain why the real impact of statins has been lower than might be predicted from the trials, along with poor compliance and that much statin use seems to be in relatively low-risk patients not included in the trials [21, 23].

Exploring PDD and PTD goes some way towards explaining the variations between countries in statins use but more needs to be done to examine use in relation to reimbursement regulations, morbidity and local medical and patient culture [2]. There is variation in use of statins not just between countries but even within countries (e.g. Italy [24]), apparently unrelated to morbidity. The variation in PDD across countries is perhaps surprising and not explained by this study. This has no basis in drug licensing since each of the drugs is licensed at the same doses across Europe [25]. Nor do the differ-

ences in the PDD among drugs seem to have any basis in evidence of effectiveness. Instead they may relate to marketing or to something as trivial as the smallest size of tablet available. If so, this is an issue to be addressed both by improving medical practice and by drug licensing.

The data and apparent variation between countries may also be explained in part by the rise in the relative use of more potent statins, particularly atorvastatin, and distorted by the use of the DDD. The DDD does not imply equipotency [26], though it has been used in this way for reimbursement in some countries [27]. For instance, pravastatin or fluvastatin at a dose equivalent to one DDD of each (20 mg and 40 mg, respectively) lowers LDL cholesterol by approximately 23% [28–31]; one DDD of simvastatin or of lovastatin [26, 27, 29] lowers it by approximately 30–31%, while for one DDD of atorvastatin (10 mg, the lowest strength tablet available), the reduction is 37% [26–28] and for rosuvastatin 42–45% [27, 28]. A given degree of cholesterol lowering may not of course translate into proportionately similar differences in clinical outcomes. Nevertheless, when therapy is increasingly oriented towards achieving a given target total cholesterol or LDL, use of more potent statins will lower cholesterol more for a smaller rise in DDDs than some of the older less potent drugs.

As statins have increased their use, other lipid lowering drugs have been far less used. However fibrates have held their market in Belgium and France and to a lesser extent in Germany. This reflects their weaker evidence base of effectiveness in lowering mortality, although that has improved in recent years [32].

Limitations of this study are the lack of availability of data in many countries or at many time points. The limitations of administrative databases and of commercial databases have been described previously [3], and include an inability to examine the targeting of statins in most but not all countries. The numbers of prescriptions used in calculating PDDs are in some cases relatively few. It is imperative that a better system of monitoring data be established: the EURO-MED-STAT project has produced a number of suggested indicators and practical proposals on this [33]. Our denominator for utilization, per 1000 inhabitants is also less satisfactory: better would have been a figure per 1000 patients at defined levels of risk, or even by age and gender, but these data are not available.

Our study does not address two recent market developments: first, generic simvastatin products are now available and are likely to be widely encouraged as a means of reducing the enormous cost of these drugs; second, we have not considered over-the-counter availability of simvastatin in countries like the UK, but there is no evidence as yet that this has impacted on prescription sales.

Extensive variation in statins use across Europe persists. The variation is explained in part by the number of patient days of treatment provided but also in an as yet unexplained variation in the doses prescribed, which seem inconsistent either with the evidence of effectiveness or with the licensing. Data are urgently awaited that would link detailed patterns of use, preferably at individual level, to cardiovascular outcomes, to reassess the effectiveness of statins relative to their costs for community and patients.

The full details of participants can be found in ref [3].

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Appendices

Appendix 1

Information sources

	EuroMedStat	IMS
AUT	Hauptverband der Österreichischen Sozialversicherungsträger/PEGASUS (Federation of Austrian Social Insurance Institutions)	
BEL	Farmanet (RijksInstituut voor Ziekte en InvaliditeitsVerzekering/Institut National d'Assurance Invalidité) (National Institute for Health and Disability Insurance)	Sample size: 500 doctors stratified by region and 15 specialities Sample design: Disproportional stratification by speciality; proportional stratification by region within each speciality Selection method: At random from address register Reporting time: 7 consecutive days within each quarter
DNK	Lægemiddelstyrelsen (Danish Medicines Agency)	
FIN	Lääkemyyntirekisteri, Lääkelaitos (Drug Sales Register owned by the National Agency for Medicines)	Sample size: 419 doctors stratified by region and 8 specialities Sample design: Stratified cluster sample Selection method: At random from address register Reporting time: 5 consecutive days per semester
FRA	Caisse Nationale d'Assurance Maladie (CNAM) base de données Médicam (National Health Insurance-database Medicam)	Sample size: 835 doctors stratified by region, 12 specialities, size of community, environment age of doctor, and sex of doctor Sample design: Random sample partially rotating (3340 doctor weeks) per year Selection method: At random out of a doctor list Reporting time: 7 consecutive days per quarter
GER	Database of the German Drug Index, Wissenschaftliches Institut der AOK (WIdO)	Sample size: >5000 doctor weeks of reporting split by 10 specialities and region Sample design: Random and stratified Selection method: At random out of a doctor list Reporting time: diary doctors: One week per quarter; electronic data practices: 3 weeks per quarter
IRL	Reimbursement files from the General Medical Services Payments Board	Sample size: 200 general practitioners, GMS & private Sample design: Stratified by region and years since qualified Selection method: At random out of a doctor list Reporting time: 6 consecutive days per quarter
ITA	Ministero della Salute-Osservatorio Nazionale sull'Impiego dei Medicinali (OsMed) (Ministry of Health – Observatory on Utilization of Medicines)	Sample size: 1486 doctors stratified by 13 specialities, region and town size Sample design: Stratified, fixed Selection method: At random out of a doctor list Reporting time: 7 consecutive days per quarter
NDL	College voor Zorgverzekeringen, Geneesmiddelen Informatie Project Amstelveen/Stichting Farmaceutische Kengetallen Den Haag (Health Care Insurance Board, Pharmaceutical Products Information Project Amstelveen/Foundation for Pharmaceutical Statistics The Hague)	Sample size: 360 doctors stratified by region, 10 specialities and four community sizes Sample design: Proportional stratification by region, community size class and speciality. Dispensing and nondispensing GPs – proportional stratification by years of qualification Selection method: At random out of a doctor list Reporting time: 7 consecutive days per quarter
NOR	Norwegian Institute of Public Health (data based on total sales from all Norwegian wholesalers)	
SPA	Agencia Española del Medicamento – Especialidades y consumo de medicamentos (Database ECOM) (Ministry of Health, Spanish Medicines Agency)	Sample size: 850 doctors of which 70% fixed, 30% rotating. Stratified by region, 18 specialities and fivecommunity sizes Sample design: Proportional stratification by region and community size. Disproportional by speciality Selection method: At random out of a doctor list Reporting time: 7 consecutive days per quarter
SWE	Apoteket – National Corporation of Swedish Pharmacies	

Appendix 1 continued

	EuroMedStat	IMS
UK	Prescription Pricing Authority (PPA)	Sample size: Fixed panel of 500 general practitioners stratified by region and age since qualification Sample design: Proportional stratification by region, community size class and speciality. Dispensing and nondispensing GPs – proportional stratification by years of qualification Selection method: At random out of users of three GP systems from one supplier Reporting time: Daily for 13 weeks in every quarter

AUT = Austria, BEL = Belgium, DNK = Denmark; FIN = Finland, FRA = France, GER = Germany, IRL = Ireland, ITA = Italy, NDL = The Netherlands, NOR = Norway, SPA = Spain, SWE = Sweden, UK = United Kingdom

Appendix 2

A: Example of calculation of patient treatment days (PTD_{2000}), France 2000

	DDD (mg)	PDD_{2000} (mg)	DDD/PDD	DDDs/1000/day	PTD_{2000}/1000/day
Atorvastatin	10	16.8	0.595	15.6	9.27
Cerivastatin	0.2	0.28	1.4	7.09	5.11
Fluvastatin	40	37.5	1.07	1.96	2.09
Pravastatin	20	20.6	0.97	9.96	9.57
Simvastatin	15	15	1	13.6	13.62
Total				48.11	39.64
Total (without cerivastatin)				41.02	34.53

B: It is possible to calculate the extent to which the increase in volume of use (measured by DDD) between 2000 and 2003 is due to an increase in PDD or an increase in number of PTD. For this, cerivastatin data are omitted from 2000 totals and rosuvastatin from 2003 because of market additions and deletions.

France	DDD/1000/day	PTD/1000/day	
2000	41.02	34.53	
2003	75.19	53.56	
% Increase	83%	55%	
% total increase due to increase in PTD			55/83 = 66%
% total increase due to increase in PDD			100–66 = 34%